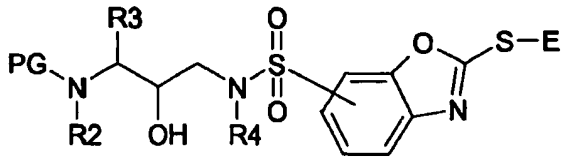
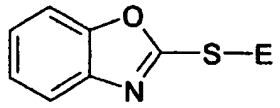
CLAIMS

1. A method for preparing a compound of formula (6),



(6)

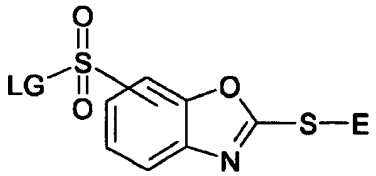
and salts, stereoisomeric forms, and racemic mixtures thereof, characterized in that said method starts from a compound of formula (2),



(2)

wherein **E** is an electrophilic moiety;

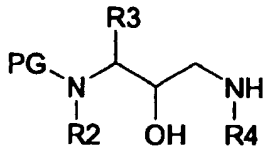
transforming compound of formula (2) into a compound of formula (3),



(3)

wherein **LG** is a leaving group; and

reacting compound of formula (3) with a compound of formula (5),



(5)

wherein

PG is a protecting group;

R_2 is hydrogen or C_{1-6}alkyl;

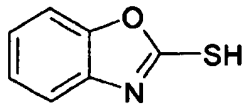
R_3 is C_{3-7}cycloalkyl, aryl, Het^1, Het^2, or C_{1-6}alkyl optionally substituted with C_{3-7}cycloalkyl, aryl, Het^1, or Het^2; wherein each C_{3-7}cycloalkyl, aryl, Het^1, and Het^2 may be optionally substituted with one or more groups selected from oxo, C_{1-6}alkyloxy, C_{1-6}alkyl,

C_{1-6}alkylsulfonyl, aminosulfonyl, amino, C_{1-6}alkylcarbonylamino, hydroxyC_{1-6}alkyl, cyano, C_{1-6}alkyloxycarbonyl, aminocarbonyl, halogen or trifluoromethyl, wherein each amino maybe mono- or disubstitued with C_{1-6}alkyl;

R_4 is selected from the group comprising hydrogen, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from aryl, Het^1, Het^2, C_{3-7}cycloalkyl, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, aminosulfonyl, C_{1-4}alkyl-S(=O)$_t$, hydroxy, cyano, halogen and amino optionally mono- or disubstituted where the substituents are each independently selected from C_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl; and

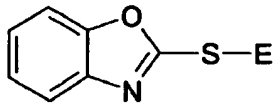
t is zero, one or two.

2. A method according to claim 1 for preparing a compound of formula (6), characterized in that said method comprises the steps of:
alkylating a compound of formula (1)



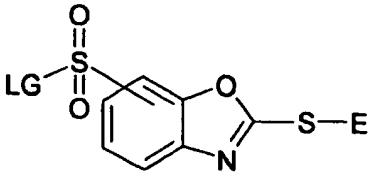
(1)

resulting into a compound of formula (2);



(2)

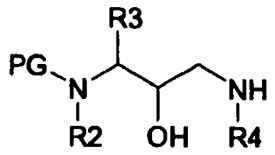
wherein E is a C_{1-6}alkyl;
reacting compound of formula (2) with a sulfonation agent, resulting in a compound of formula (3);



(3)

wherein LG is a leaving group; and

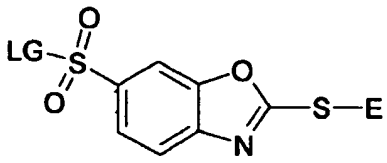
coupling compound of formula (3) with a compound of formula (5).



(5)

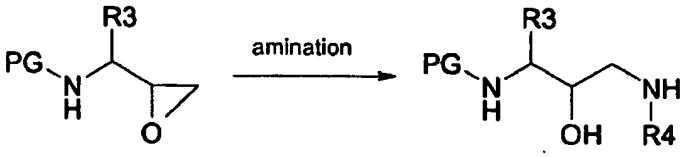
wherein **PG** is a protecting group; and
wherein R_2, R_3, and R_4 are as claimed in claim 1.

3. A method according to any one of claims 1 to 2, characterized in that compound of formula (3) is a compound of formula (3''').



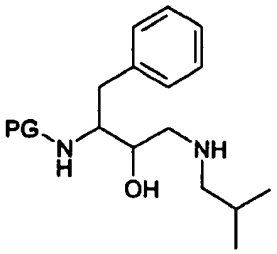
(3''')

4. A method according to any one of claims 1 to 3, characterized in that compound of formula (5) is obtained by amination of an epoxide-containing compound of formula (4), and the amination reagent is H_2N-R_4, wherein R_4 is as claimed in any one of claims 1 to 3.



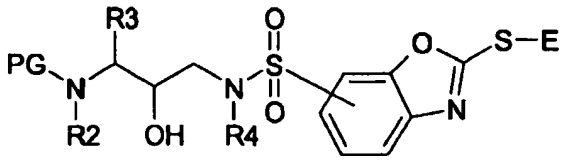
(4) (5)

5. A method according to any one of claims 1 to 4, wherein compound of formula (5) is compound of formula (5').



(5')

6. A compound having formula (6)



(6)

and salts, stereoisomeric forms, and racemic mixtures thereof, characterized in that **PG**, R_2, R_3, R_4, and **E** are as defined in any one of claims 1 to 5.

7. A compound according to claim 6, characterized in that

R_2 is hydrogen;

R_3 is arylC_{1-4}alkyl, arylmethyl, or phenylmethyl;

R_4 is unsubstituted C_{1-6}alkyl or C_{1-6}alkyl substituted with one or more substituents selected from aryl, Het^1, Het^2, C_{3-7}cycloalkyl and amino optionally mono- or disubstituted where the substituents are selected from C_{1-4}alkyl, aryl, Het^1 and Het^2.

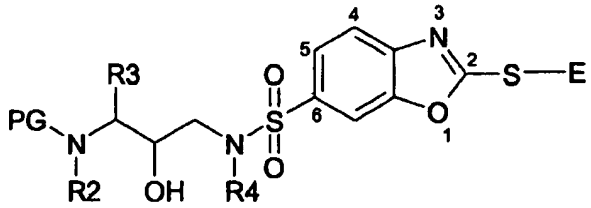
8. A compound according to any one of claims 6 to 7, characterized in that

R_2 is hydrogen;

R_3 is phenylmethyl; and

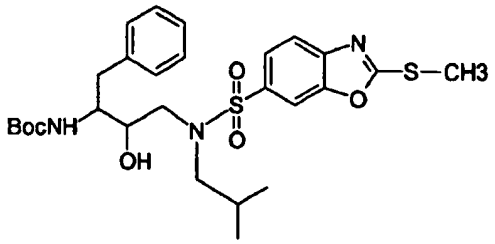
R_4 is isobutyl.

9. A compound according to any one of claims 6 to 8, characterized in that the compound has formula (6'').



(6'')

10. A compound according to any one of claims 6 to 9, characterized in that the compound has formula (6''').

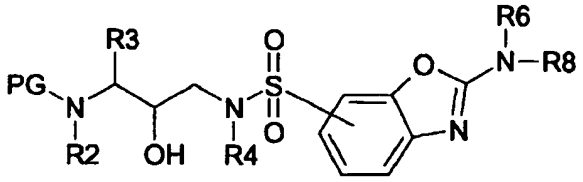


(6''')

11. A compound according to any one of claims 6 to 10, characterized in that said compound is in the form of a salt selected from trifluoroacetate, fumarate, chloroacetate and methanesulfonate.

12. A method for preparing a compound of formula (9), wherein said method comprises the methods according to any one of claims 1 to 5, characterised in that said method further comprises

aminating compound of formula (6) to obtain compound of formula (7), wherein



(7)

R_6 is hydrogen, hydroxy, C_{1-6}alkyl, Het^1C_{1-6}alkyl, Het^2C_{1-6}alkyl, aminoC_{1-6}alkyl whereby the amino group may optionally be mono-or di-substituted with C_{1-4}alkyl;

R_8 is hydrogen, C_{1-6}alkyl, or -A-R_7;

A is C_{1-6}alkanediyl, -C(=O)-, -C(=S)-, -$S(=O)_2$-, C_{1-6}alkanediyl-C(=O)-, C_{1-6}alkanediyl-C(=S)- or C_{1-6}alkanediyl-$S(=O)_2$-; whereby the point of attachment to the nitrogen atom is the C_{1-6}alkanediyl group in those moieties containing said group;

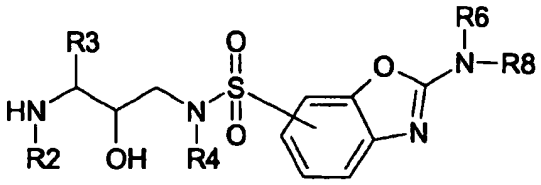
R_7 is C_{1-6}alkyloxy, Het^1, Het^1oxy, Het^2, Het^2oxy, aryl, aryloxy, C_{3-7}cycloalkyl, or optionally mono- or disubstituted amino; and

in case -A- is other than C_{1-6}alkanediyl then R_7 may also be C_{1-6}alkyl, Het^1C_{1-4}alkyl, Het^1oxyC_{1-4}alkyl, Het^2C_{1-4}alkyl, Het^2oxyC_{1-4}alkyl, arylC_{1-4}alkyl, aryloxyC_{1-4}alkyl or amino-C_{1-6}alkyl; whereby each of the amino groups in the definition of R_7 may optionally be substituted with one or more substituents selected from C_{1-4}alkyl, C_{1-4}alkylcarbonyl, C_{1-4}alkyloxycarbonyl, aryl, arylcarbonyl, aryloxycarbonyl, Het^1, Het^2, arylC_{1-4}alkyl, Het^1-C_{1-4}alkyl or Het^2C_{1-4}alkyl ; and

-A-R_7 may also be hydroxyC_{1-6}alkyl; and

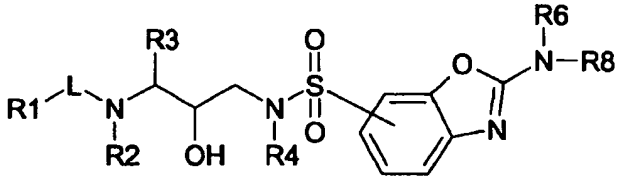
R_6 and -A-R_7 taken together with the nitrogen atom to which they are attached may also form Het^1 or Het^2;

deprotecting compound of formula (7) to obtain compound of formula (8),



(8)

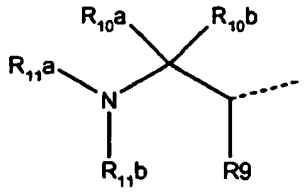
coupling a radical of formula R_1-L- to obtain compound of formula (9),



(9)

and *N*-oxides, salts, stereoisomeric forms, racemic mixtures, prodrugs, esters and metabolites thereof, wherein

R_1 is selected from the group comprising hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, arylC_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, aryl, Het^1, Het^1C_{1-6}alkyl, Het^2, Het^2C_{1-6}alkyl; and R_1 may also be a radical of formula (10)



(10)

R_9, R_{10a} and R_{10b} are, each independently, hydrogen, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl optionally substituted with aryl, Het^1, Het^2, C_{3-7}cycloalkyl, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)-aminocarbonyl, aminosulfonyl, C_{1-4}alkylS(O)$_t$, hydroxy, cyano, halogen or amino optionally mono- or disubstituted where the substituents are each independently selected from C_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and

Het^2C_{1-4}alkyl; whereby R_9, R_{10a} and the carbon atoms to which they are attached may also form a C_{3-7}cycloalkyl radical;

when L is -O–C_{1-6}alkanediyl-C(=O)- or –NR_{12}-C_{1-6}alkanediyl-C(=O)-, **then R_9** may also be oxo;

$\mathbf{R_{11a}}$ is selected from the group comprising hydrogen, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, aryl, aminocarbonyl optionally mono- or disubstituted, aminoC_{1-4}alkylcarbonyloxy optionally mono- or disubstituted, C_{1-4}alkyloxycarbonyl, aryloxycarbonyl, Het^1oxycarbonyl, Het^2oxycarbonyl, aryloxycarbonylC_{1-4}alkyl, arylC_{1-4}alkyloxycarbonyl, C_{1-4}alkylcarbonyl, C_{3-7}cycloalkylcarbonyl, C_{3-7}cycloalkyl-C_{1-4}alkyloxycarbonyl, C_{3-7}cycloalkylcarbonyloxy, carboxylC_{1-4}alkylcarbonyloxy, C_{1-4}alkylcarbonyloxy, arylC_{1-4}alkylcarbonyloxy, arylcarbonyloxy, aryloxycarbonyloxy, Het^1carbonyl, Het^1carbonyloxy, Het^1C_{1-4}alkyloxycarbonyl, Het^2carbonyloxy, Het^2C_{1-4}alkylcarbonyloxy, Het^2C_{1-4}alkyloxycarbonyloxy or C_{1-4}alkyl optionally substituted with aryl, aryloxy, Het^2 or hydroxy; wherein the substituents on the amino groups are each independently selected from C_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl
C_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl;

$\mathbf{R_{11b}}$ is selected from the group comprising hydrogen, C_{3-7}cycloalkyl, C_{2-6}alkenyl,
C_{2-6}alkynyl, aryl, Het^1, Het^2 or C_{1-4}alkyl optionally substituted with halogen, hydroxy, C_{1-4}alkylS(=O)$_t$, aryl, C_{3-7}cycloalkyl, Het^1, Het^2, amino optionally mono- or disubstituted where the substituents are each independently selected from C_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl;

whereby $\mathbf{R_{11b}}$ may be linked to the remainder of the molecule via a sulfonyl group; and

L is selected from the group comprising -C(=O)-, -O-C(=O)-, -NR_{12}-C(=O)-, -O–C_{1-6}alkanediyl-C(=O)-, -NR_{12}-C_{1-6}alkanediyl-C(=O)-, -S(=O)$_2$-, -O-S(=O)$_2$-, -NR_{12}-S(=O)$_2$ whereby either the C(=O) group or the S(=O)$_2$ group is attached to the NR_2 moiety; whereby the C_{1-6}alkanediyl moiety is optionally substituted with a substituent selected from hydroxy, aryl, Het^1, and Het^2;

$\mathbf{R_{12}}$ is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, arylC_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, aryl, Het^1, Het^1C_{1-6}alkyl, Het^2, Het^2C_{1-6}alkyl;

$\mathbf{R_2}$ is hydrogen or C_{1-6}alkyl;

$\mathbf{R_3}$ is C_{3-7}cycloalkyl, aryl, Het^1, Het^2, or C_{1-6}alkyl optionally substituted with C_{3-7}cycloalkyl, aryl, Het^1, or Het^2; wherein each C_{3-7}cycloalkyl, aryl, Het^1, and Het^2 may be optionally substituted with one or more groups selected from oxo, C_{1-6}alkyloxy, C_{1-6}alkyl,

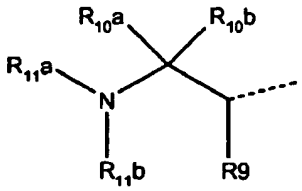
C_{1-6}alkylsulfonyl, aminosulfonyl, amino, C_{1-6}alkylcarbonylamino, hydroxyC_{1-6}alkyl, cyano, C_{1-6}alkyloxycarbonyl, aminocarbonyl, halogen or trifluoromethyl, wherein each amino maybe mono- or disubstitued with C_{1-6}alkyl;

R_4 is selected from the group comprising hydrogen, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{1-6}alkyl optionally substituted with one or more substituents each independently selected from aryl, Het^1, Het^2, C_{3-7}cycloalkyl, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, aminosulfonyl, C_{1-4}alkyl-S(=O)$_t$, hydroxy, cyano, halogen and amino optionally mono- or disubstituted where the substituents are each independently selected from C_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl; and

t is zero, one or two.

13. The method according to claim 12, wherein

R_1 is a radical of formula (10)



(10)

R_9, R_{10a} and R_{10b} are, each independently, hydrogen, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl optionally substituted with aryl, Het^1, Het^2, C_{3-7}cycloalkyl, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)-aminocarbonyl, aminosulfonyl, C_{1-4}alkylS(O)$_t$, hydroxy, cyano, halogen or amino optionally mono- or disubstituted where the substituents are each independently selected from C_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl-C_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl;

whereby R_9, R_{10a} and the carbon atoms to which they are attached may also form a C_{3-7}cycloalkyl radical;

R_{11b} is hydrogen, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl, Het^1, Het^2 or C_{1-4}alkyl optionally substituted with halogen, hydroxy, C_{1-4}alkylS(=O)$_t$, aryl, C_{3-7}cycloalkyl, Het^1, Het^2, amino optionally mono- or disubstituted where the

substituents are each independently selected from C_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl;

whereby R_{11b} may be linked to the remainder of the molecule via a sulfonyl group;

t is zero, one or two;

L is -C(=O)-, -O-C(=O)-, -NR_{12}-C(=O)-, -O-C_{1-6}alkanediyl-C(=O)-, -NR_{12}-C_{1-6}alkanediyl-C(=O)-, -S(=O)$_2$-, -O-S(=O)$_2$-, -NR_{12}-S(=O)$_2$ whereby either the C(=O) group or the S(=O)$_2$ group is attached to the NR_2 moiety; whereby the C_{1-6}alkanediyl moiety is optionally substituted with a substituent selected from hydroxy, aryl, Het^1, and Het^2;

R_{12} is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, arylC_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, aryl, Het^1, Het^1C_{1-6}alkyl, Het^2, Het^2C_{1-6}alkyl; and

R_4 is hydrogen, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, or C_{1-6}alkyl optionally substituted with one or more substituents selected from aryl, Het^1, Het^2, C_{3-7}cycloalkyl, C_{1-4}alkyloxycarbonyl, carboxyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)-aminocarbonyl, aminosulfonyl, C_{1-4}alkylS(=O)$_t$, hydroxy, cyano, halogen and amino optionally mono- or disubstituted where the substituents are selected from C_{1-4}alkyl, aryl, arylC_{1-4}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl–C_{1-4}alkyl, Het^1, Het^2, Het^1C_{1-4}alkyl and Het^2C_{1-4}alkyl.

14. The method according to any one of claims 12 to 13, wherein one or more of the following restrictions apply:

R_1 is hydrogen, Het^1, Het^2, aryl, Het^1C_{1-6}alkyl, Het^2C_{1-6}alkyl, arylC_{1-6}alkyl, more in particular, R_1 is a saturated or partially unsaturated monocyclic or bicyclic heterocycle having 5 to 8 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulfur and which is optionally substituted, or phenyl optionally substituted with one or more substituents;

R_2 is hydrogen;

L is -C(=O)-, -O-C(=O)-, -O–C_{1-6}alkanediyl-C(=O)-, more in particular, L is -O-C(=O)- or -O–C_{1-6}alkanediyl-C(=O)-, whereby in each case the C(=O) group is attached to the NR_2 moiety;

R_3 is arylC_{1-4}alkyl, in particular, arylmethyl, more in particular phenylmethyl;

R_4 is optionally substituted C_{1-6}alkyl, in particular unsubstituted C_{1-6}alkyl or C_{1-6}alkyl optionally substituted with one or more substituents selected from aryl, Het^1, Het^2, C_{3-7}cycloalkyl and amino optionally mono- or disubstituted where the substituents are selected from C_{1-4}alkyl, aryl, Het^1 and Het^2;

R_6 is hydrogen or methyl; and

R_8 is hydrogen or methyl.

15. The method according to any one of claims 12 to 14, wherein

R_1-L is Het^1-O-C(=O), Het^2-C_{1-6}alkanediyl-O-C(=O), aryl-O-C_{1-6}alkanediyl-C(=O) or aryl—C(=O).

16. The method according to any one of claims 12 to 15, wherein

NR_6R_8 is amino, monomethylamino or dimethylamino.

17. The method according to to any one of claims 12 to 16, wherein

R_1 is a Het^1, or a Het^1C_{1-6}alkyl, and

L is –O-C(=O)-;

R_2 is hydrogen;

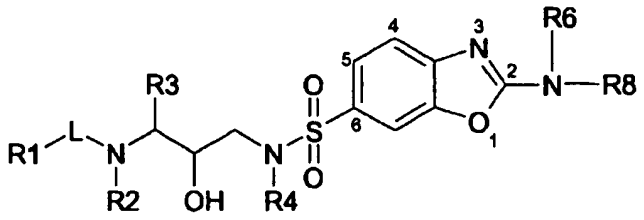
R_3 is phenylmethyl;

R_4 is isobutyl;

R_6 is hydrogen; and

R_8 is hydrogen or methyl.

18. The method according to any one of claims 12 to 17, wherein compound (9) has formula (9''').



(9''')

19. The method according to any one of claims 12 to 18, characterized in that compound of formula (9) is in the form of a salt selected from trifluoroacetate, fumarate, chloroacetate and methanesulfonate.

20. Use of a compound as claimed in any of claims 7 to 11 as an intermediate for preparing a retrovirus protease inhibitor of formula (9).

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